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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,644	11/26/2008	John P. Toscano III	P30955US02/20642.034	2708

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EXAMINER	
THOMAS, TIMOTHY P	
ART UNIT	**PAPER NUMBER**
1628	

NOTIFICATION DATE	DELIVERY MODE
02/28/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IP.Docketing@aporter.com

Office Action Summary	Application No.	Applicant(s)	
	10/587,644	TOSCANO ET AL.	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,15,17-41 and 47-50* is/are pending in the application.

4a) Of the above claim(s) *17-41 and 47-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____

DETAILED ACTION

Response to Arguments

1. Applicants' arguments, filed 12/22/2010 have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

2. Applicant's arguments, see pp. 8-9, filed 12/22/2010, with respect to the rejection under 35 USC 112, 2nd paragraph have been fully considered and are persuasive. The rejection of claims 1, 15-16 and 43 has been withdrawn.

3. Applicant's arguments, see p. 9, filed 12/22/2010, with respect to the written description rejection have been fully considered and are persuasive. The rejection of claim 1 has been withdrawn.

4. Applicant's arguments, see pp. 9-10, filed 12/22/2010, with respect to the enablement rejection have been fully considered and are persuasive. The rejection of claim 1 has been withdrawn.

5. Applicant's arguments, see pp. 10-11, filed 12/22/2010, with respect to the anticipation rejection have been fully considered and are persuasive. The rejection of claims 1, 15-16 and 43 has been withdrawn.

The amendment to claim 1 removes the option for R^1 and R^2 to be unsubstituted alkyl, which the Fitzhugh compounds read on. None of the compounds taught by Fitzhugh anticipate the currently amended claims; therefore, the rejection basis is withdrawn.

6. Applicant's arguments with respect to the enablement rejection have been fully considered but they are not persuasive:

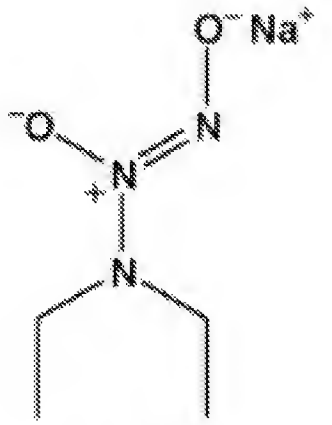
Claims 1 and 15 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Fitzhugh et al. ("Qualitative Thin-Layer and High-Performance Liquid Chromatographic Analysis of 1-Substituted Diazen-1-ium-1,2-diolates on Aminopropyl-Bonded Silica Gel"; 2002; Analytical Biochemistry; 301: 97-102; IDS 3/26/2010 reference BJ1); in view of Patani et al. ("Bioisosterism: A Rational Approach in Drug Design"; 1996; Chem. Rev.; 96: 3147-3176) and Ismail ("Important fluorinated drugs in experimental and clinical use"; 2002; Journal of Fluorine Chemistry; 118: 27-33).

The rejection is maintained for the reasons of record. It is noted that claims 16 and 43 are canceled by the claim amendment.

Applicant argues the evidence and arguments of record provide no suggestion or reason for a person of ordinary skill in the art to select the specific "lead compound" and the specific structural modifications that would be necessary to make applicant's claims compounds; that while Fitzhugh mentions the use of diazeniumdiolates as nitric oxide donors, the article focuses on HPLC and TLC methods for detecting and quantifying diazeniumdiolates; that nowhere does Fitzhugh suggest that compound 2 is particularly effective NO donor as compared to all other known NO donors, including the remaining compounds disclosed in Fitzhugh; that the cited art offers no suggestion or reason for an ordinarily skilled artisan to consider any of Fitzhugh's compounds, let alone compound 2 as a starting point for developing new NO donors.

It is noted that the facts of *Sanofi-Synthelabo v. Apotex* involve a different fact pattern than the instant case; the instant rejection is not based on separating stereoisomers over a prior art teaching of a racemate, as is the decision rendered in *Sanofi*. With respect to the statement made in *Sanofi* that a *prima face* case of obviousness depends on whether the prior art provides a suggestion or reason to choose a specific lead compound for modificiation, such a suggestion and reason to select compound 2, based on the teachings of Fitzhugh, is of record. The record indicates that Fitzhugh teaches:

> diazeniumdiolates, compounds containing the anionic $R_2N[N(O)NO]^-$ moiety, are receiving increasing use as nitric oxide (NO) donors in chemical and biochemical studies; the release of NO in such settings produces pharmacological effects including cytostasis, vasodilation, penile erection, etc.; these remarkable properties have generated considerable interest in the potential further use of diazeniumdiolates as therapeutic agents, particularly in the treatment of such important clinical disorders as pulmonary hypertension, cerebral vasospasm, impotence and thrombosis at blood-contact surfaces (p. 97, 1st paragraph). Compounds specifically taught include: …



2

This teaching establishes the Fitzhugh compounds are nitric oxide donors in chemical and biochemical studies; that release of NO provides pharmacological effects, including cytostasis, vasodilation, penile erection, etc; that the compounds have considerable interest in potential further use as therapeutic agents, in treatment of pulmonary hypertension, cerebral vasospasm, impotence and thrombosis at blood-contact surfaces. These biological properties and potential therapeutic applications, which provide suggestion for selection and provide a reason to select the Fitzhugh compounds, are an articulated rationale by Fitzhugh for selection of any one of the 7 compounds specifically taught by Fitzhugh, including compound 2, as a "lead compound", for further modification.

With respect to the implication that there is a requirement for the selection of only compound 2, this is inconsistent with *Proctor & Gamble v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 989 (Fed. Cir 2009), which makes clear it is not necessary to select a single compound as a "lead compound" in order to support an obviousness rejection. *Altana Pharma AG v. Teva Pharms. USA*, Inc. 566 F.3d 999 (Fed. Cir. 2009) indicates

that obviousness of a chemical compound (the elected compound) in view of its structural similarity to a prior art compound (compound 2 of Fitzhugh) may be shown by identifying some line of reasoning that would have led one of ordinary skill in the art to select and modify a prior art lead compound in a particular way to produce the claimed compound; that it is not necessary for the reasoning to be explicitly found in the prior art of record, nor is it necessary for the prior art to point to only a single lead compound.

Accordingly, such a line of reasoning had been established for the selection of any one of the 7 compounds specifically exemplified by Fitzhugh, including compound 2, based on the properties and potential therapeutic uses of the compounds taught.

The record has also established a line of reasoning that would have led one of ordinary skill in the art to modify a prior art lead compound in a particular way to produce the claimed compound. The record indicates Patani teaches:

> Classical bioisosteres include the substitution of hydrogen by fluorine, which is one of the more commonly employed monovalent isosteric replacemic; steric parameters for hydrogen and fluorine are similar, the difference in the electronic effects is often the basis for the major differences in the pharmacological properties of agents where fluorine has been substituted for hydrogen (p. 3149, 5th paragraph). This reference provides motivation to substitute F for H in an active compound in an attempt to find a safer and/or more effective agent than the starting compound.

The record also indicates Ismail teaches:

fluorine imparts desirable characteristics to drugs by modulating both the pharmacokinetics and pharmacodynamic properties of a drug; incorporation of fluorine into a drug increases the lipophilicity enhancing absorption into biological membranes whereby its small covalent radius can facilitate docking with their drug receptor(s) (abstract); bioisosteric substitution of hydrogen by fluorine is, therefore, an important strategy for incorporation of a group capable of reinforcing drug-receptor interactions, aiding translocation across lipid bilayers or absorption (p. 27, 2nd paragraph). Specific groups taught in molecules include trifluoromethyl groups (p. 28, right, 2nd paragraph; see also examples in compounds (8), which has two trifluoromethyl moieties and (9) (p. 28). This reference provides motivation to utilize trifluoromethyl groups in active compounds for the purposes taught by Ismail.

The motivation of record indicates:

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute the terminal methyl hydrogens of the ethyl moieties of compound 2 taught by Fitzhugh, with fluorine atoms to give trifluoromethyl moieties, where the R groups of the diazeniumdiolate compound corresponds to $-CH_2CF_3$, i.e., the instant elected compound. The motivation would have been the expectation of increased lipophilicity enhancing absorption and/or improved translocation across membranes to a target location.

Therefore, the requirement of *Altana* to establish a line of reasoning that would have led one of ordinary skill in the art to select and modify a prior art lead compound in a particular way to produce the claimed compound for a has been met

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant further argues that Patani discloses a multitude of bioisosteres; that somehow one of skill in the art would not have singled out fluorine replacement as the sole means for modifying Fitzhugh's compound. A "sole means for modifying" is not the requirement of *Altana*, but identifying some line of reasoning that would have led one of ordinary skill in the art to select and modify a prior art lead compound in a particular way to produce the claimed compound, has been established. It is further noted that Patani indicates the F/H substitution is one of the more commonly employed monovalent isosteric replacemics; and Ismail, which is primarily concerned with fluorine substitution, teaches fluorine imparts desirable characteristics to drugs by modulating both the pharmacokinetics and pharmacodynamic properties of a drug; incorporation of fluorine into a drug increases the lipophilicity enhancing absorption into biological membranes

whereby its small covalent radius can facilitate docking with their drug receptor(s); Ismail clearly gives the examples of bioisosteres having a single trifluoromethyl and even two separate trifluoromethyl groups in the same compound, rendering the specific modification obvious.

Applicant argues that Ismail fails to overcome the deficiencies of Patani; somehow the articulated teaching of Ismail is argued to fail to provide any suggestion or reason to modify any one of Fitzhugh's compound in the precise manner that would be necessary to produce applicant's claimed compounds. This is not persuasive; the teaching of Patani and Ismail have been repeated above, along with the required modification necessary to arrive at the instant elected compound. Therefore the rejection is maintained.

Conclusion

7. No claim is allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY P. THOMAS whose telephone number is (571)272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on (571) 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Timothy P Thomas/
Primary Examiner, Art Unit 1628